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Acute Aortic Dissections with Pregnancy in Women with *ACTA2* Mutations

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Abstract

Mutations in *ACTA2* predispose to thoracic aortic aneurysms and dissections as well as coronary artery and cerebrovascular disease. Here we examined the risk of aortic dissections, stroke and myocardial infarct with pregnancy in women with *ACTA2* mutations. Of the 53 women who had a total of 137 pregnancies, eight had aortic dissections in the third trimester or the postpartum period (6% of pregnancies). One woman also had a myocardial infarct that occurred during pregnancy that was independent of her aortic dissection. Compared to the population-based frequency of peripartum aortic dissections of 0.6%, the rate of peripartum aortic dissections in women with *ACTA2* mutations is much higher (8 out of 39; 20%). Six of these dissections initiated in the ascending aorta (Stanford type A), three of which were fatal. Three women had ascending aortic dissections at diameters less than 5.0 cm (range 3.8 to 4.7 cm). Aortic pathology showed mild to moderate medial degeneration of the aorta in three women. Of note, five of the women had hypertension either during or before the pregnancy. In summary, the majority of women with *ACTA2* mutations did not have aortic or other vascular complications with pregnancy. However, these findings show that pregnancy is associated with significant risk for aortic dissections in women in whom diagnosis of *ACTA2* mutation has not been made. Women with *ACTA2* mutations who are planning to get pregnant should be counseled about this risk of aortic dissections, and proper clinical management should be initiated to reduce this risk.

Keywords

ACTA2; aortic dissection; stroke; myocardial infarct; pregnancy

INTRODUCTION

Hemodynamic changes, such as increased intravascular volume, heart rate, and cardiac output occur during pregnancy. These changes are believed to be responsible for the increased risk for acute aortic dissections during pregnancy, and this risk is particularly high in women who have single gene mutations predisposing them to thoracic aortic aneurysms leading to aortic dissections (TAAD) [Mashini et al., 1987; Milewicz et al., 2008a; Poppas et al., 1997]. For example, individuals with Marfan syndrome have progressive and asymptomatic enlargement of the aorta at the level of the sinuses of Valsalva (termed aortic root aneurysms) that can lead to life-threatening acute aortic dissections. Aortic disease in patients with Marfan syndrome is managed by initiating beta adrenergic blockers, monitoring the size of the aneurysm with serial imaging, and surgically repairing the aneurysm when the aortic root diameter reaches 5.0 to 5.5. cm [Hiratzka et al., 2010]. Using this protocol, acute aortic dissections in patients with MFS can be prevented and the life expectancy extended [Silverman et al., 1995]. Retrospective studies of women with Marfan syndrome have shown 4–7 % of pregnancies were complicated by aortic dissection or rapid aortic root dilatation [Lind and Wallenburg, 2001; Lipscomb et al., 1997; Pacini et al., 2009], while prospective studies indicate this risk is low in women with aortic root enlargement less than 4.0 cm or 4.5 cm [Meijboom et al., 2005; Rossiter et al., 1995].

Other single gene mutations predispose to thoracic aortic aneurysms leading to aortic dissections in families in the absence of syndromic features, termed familial TAAD [Milewicz et al., 2008b]. The most commonly altered gene causing familial TAAD is *ACTA2* which is responsible for 10 - 14% of familial disease [Disabella et al., 2011; Guo et al., 2007; Hoffjan et al., 2011; Morisaki et al., 2009; Renard et al., 2013]. In addition to TAAD, individuals with certain *ACTA2* mutations are also at risk for early onset coronary artery disease, stroke, and cerebrovascular disease [Guo et al., 2009; Milewicz et al., 2010]. The risk of aortic dissection and other vascular complications in pregnant women with *ACTA2* mutations is not known, although there have been a few reports of ascending and descending dissections during pregnancy in women with *ACTA2* mutations [Morisaki et al., 2009; Yoo et al., 2010]. To understand the risk of vascular disease associated with pregnancy in women with *ACTA2* mutations, we performed a retrospective review of medical records of women with *ACTA2* mutations to examine the frequency of aortic dissections, myocardial infarction, and stroke during pregnancy and the postpartum period.

MATERIALS AND METHODS

This study was approved by the University of Texas Health Science Center at Houston Institutional Review Board, and proper informed consent was obtained from study participants. Individuals who were diagnosed with an *ACTA2* mutation by our research laboratory or a DNA diagnostic laboratory and their relatives who are obligate carriers or had a 50% risk of inheriting the *ACTA2* mutation and affected with aortic disease, were included in this study. Demographic data, finding of aortic and vascular disease including stroke and myocardial infarct, age at diagnosis, echocardiographic and radiologic findings, surgical and medical management, outcome, and medical history were extracted from the medical records (E.S.R and D.M.M.). Thoracic aortic dissections were classified based on

the Stanford classification as Type A (aortic dissections initiating in the ascending aorta that may extend to the descending aorta) or B (aortic dissections that do not involve the ascending aorta and initiating in the descending thoracic aorta just distal to the origin of the left subclavian artery). When available, computed tomography (CT) and echocardiographic images were independently read by a cardiothoracic surgeon with expertise in aortic disease (A.L.E.). Aortic measurements at different anatomical positions were obtained. Surgical pathology materials were obtained and stained with H&E and Movat's pentachrome stains and examined by L.M.B., D.G., and D.M.M. Data was analyzed and categorical variables were presented in frequencies and percentages.

RESULTS

Fifty-three women with *ACTA2* mutations had a total of 137 delivered pregnancies. Eight of these women had an acute aortic dissection during pregnancy or in the postpartum period. Thus, 6% of the pregnancies were complicated by acute aortic dissections. Four of the women experienced the aortic dissection during the third trimester at 28–37 weeks gestation and underwent emergency cesarean section, followed by surgical repair of the aorta. The other four women had dissections in the postpartum period at 6–14 days after delivery. There were no fetal deaths in these cases. Three of the women had never been pregnant, one had been pregnant once, three had been pregnant twice, and one had been pregnant three times without vascular complications.

In our cohort of individuals with *ACTA2* mutations, 39 women had thoracic aortic dissections and thus 20% of dissections (8 out of 39) were associated with pregnancy. The eight women were 29 to 43 years old (mean 34.5 years) at the time of dissection. Six of the women had type A aortic dissections and one had a type B aortic dissection. Patient 5 had an unspecified dissection that required graft replacement of the abdominal aorta and was assumed to be a type B dissection. CT imaging studies at the time of presentation were available for three women who had type A dissections (Patients 2, 7 and 8). These images showed the maximal aortic diameters to be 4.2 cm (ascending aorta), 4.7 cm (aortic root), and 3.8 cm (ascending aorta), respectively (Figure 1).

All women presented directly or were transferred to a tertiary care facility immediately after onset of symptoms. Limited medical records were available for Patients 4 and 5. But of the six women with complete records, all women presented with severe and sudden onset of pain in the chest, back, neck and/or abdomen. Pulse deficits, syncope, hypotension, hypertension and neurological deficits were also noted in some of the women at presentation (Table 1). All six women with type A dissections underwent emergency surgery and replacement of the ascending aorta, but three women died of post-operative complications. The death certificate of Patient 4 indicated the cause of death as dissecting aneurysm of the aortic arch and post-operative cerebral thrombosis. Patient 6 presented to the emergency department at 31 weeks gestation with sudden onset of chest pain and hypotension and was found to have proximal dissection and severe aortic insufficiency by cardiac catheterization. She underwent emergency cesarean section, followed by surgical repair of the ascending aorta but died post-operatively. Patient 3 presented to the emergency department at 28 weeks gestation after she complained of back pain and collapsed at home. She had no

femoral pulses on exam and underwent femoral embolectomies and femoral to femoral bypass, followed by an emergency cesarean section. An intraoperative transesophageal echocardiogram revealed a thoracic aortic dissection, which prompted transfer to another facility where she underwent repair of the ascending aorta but died of complications post-operatively.

Two of the eight women who underwent surgical repair also had a cerebrovascular event, which may have been a complication of the dissection or surgery. Patient 5 had an anteroseptal myocardial infarction in the last trimester of pregnancy and prior to a type B aortic dissection postpartum. Patient 7 had a previous myocardial infarction that was treated with percutaneous transluminal coronary angioplasty of the left anterior descending artery at the age of 41 years, two years before she presented with an aortic dissection.

Two women were hypertensive at the time of presentation and were admitted for evaluation of toxemia. Several days later, these women complained of chest, back or epigastric pain and were subsequently found to have thoracic aortic dissections. Another woman was diagnosed with postpartum pre-eclampsia. Two other women had a previous history of hypertension, but were not taking medication for hypertension during the pregnancy.

None of these women were diagnosed with an *ACTA2* mutation prior to their dissections. Despite the fact that six of the women had a family history of aortic dissections, none of them were being monitored for aortic disease. Genetic testing of these women identified the following *ACTA2* mutations: c.116G>A (p.Arg39His), c.115C>T (p.Arg39Cys), c.145A>G (p.Met49Val), c.445C>T (p.Arg149Cys), c.824G>C (p.Gly275Ala), and c.904T>G (p.Ser302Ala) (Table 1). Except for *ACTA2* mutations resulting in p.Gly275Ala and p.Ser302Ala, the rest of the mutations have been previously reported in multiple individuals with thoracic aortic aneurysms and dissections and other vascular diseases [Guo et al., 2007; Guo et al., 2009; Morisaki et al., 2009]. Gly275Ala and Ser302Ala alter highly conserved residues and were not found in in-house controls and the exome sequencing databases. The p.Gly275Ala substitution is predicted to be damaging by Polyphen-2 analysis. The p.Ser302Ala substitution is predicted to be benign; however, familial studies showed that this mutation was present in the proband (Patient 8) and her father who had a thoracic aortic dissection at the age of 45 years, and more recent brain imaging of the patient demonstrated typical features of cerebrovascular disease associated with *ACTA2* mutations, i.e. mild narrowing of the supraclinoid internal carotid arteries and periventricular hyperdense lesions [Milewicz et al., 2010; Munot et al., 2012].

The ascending thoracic aortic pathology was reviewed for Patients 2, 7 and 8 (Figure 2A). The H&E stained aortas were significant for mild to moderate medial degeneration defined by loss of smooth muscle cells and elastic fibers, and proteoglycan accumulation in the medial layer of the aorta. Aorta from Patient 2 demonstrated little to no loss of smooth muscle cells and elastin fibers but had diffuse deposition of proteoglycans. Similarly, aorta from Patients 7 and 8 had significantly more proteoglycan deposition but also have elastic fiber fragmentation and loss of smooth muscle cells (Figure 2A). It has been previously reported that the arteries in the outer layer of the aorta (termed vasa vasorum) can be

occluded or stenotic in patients with *ACTA2* mutations, and stenosis of these arteries was also observed in one of the patients (Figure 2B).

DISCUSSION

Of the 53 women with *ACTA2* mutations who had a total of 137 delivered pregnancies, only 8 women had an aortic dissection during pregnancy or postpartum (6% of pregnancies). The majority of these dissections were type A (6 out of 8), half of which were fatal. Only one woman had other vascular disease that occurred independent of the dissection, which was a myocardial infarct during the third trimester. Thus, the majority of women with *ACTA2* mutations had pregnancies without aortic or vascular complications. These findings are similar to those reported for women with Marfan syndrome, in which 4–7% of pregnancies are complicated by either rapid aortic root enlargement or acute aortic dissections, including both type A and type B dissections [Lind and Wallenburg, 2001; Lipscomb et al., 1997; Pacini et al., 2009]. However, compared to the population-based frequency of peripartum dissections of 0.6% (2 of 346) [Nienaber et al., 2004], the frequency of peripartum aortic dissections in women with *ACTA2* mutations is significantly greater (20%; 8 of 39).

CT imaging revealed that three women in this series experienced type A dissections with minimal dilatation of the ascending aorta, with a type A dissection occurring at an aortic diameter of only 3.8 cm. There have been at least two reports of women with *ACTA2* mutations and pregnancy related aortic dissections in the literature. Additionally, a 28-year-old woman with an *ACTA2* p.Asp26Tyr substitution had a type A aortic dissection late in the pregnancy, and the aortic root diameter measured only 3.5 cm [Yoo et al., 2010].

Five of the women in this report were hypertensive at presentation or had a previous history of hypertension. Hypertension is an established risk factor for aortic dissections [Januzzi et al., 2004]; [LeMaire and Russell, 2011]. We can speculate that hypertension and the increased intravascular volume of pregnancy can trigger aortic dissections at small aortic diameters in individuals with *ACTA2* mutations. In addition, the aortic pathology indicated that these dissections occurred with minimal medial degeneration of the aorta. The common pathologic feature in these patients with acute dissections was increased proteoglycan accumulation in the medial layer of the aorta. Interestingly, accumulation of proteoglycans in the medial layer has been proposed to decrease tensile strength of the aorta and predispose to local delamination within the media that could help to propagate a dissection [Humphrey, 2013; Rocca Bianca et al., 2013].

Eight genes predisposing to thoracic aortic aneurysms and acute aortic dissections have been identified so far: *ACTA2* (α -actin; MIM 102620), *MYH11* (myosin heavy chain; MIM 160745), *MYLK* (myosin light chain kinase; MIM 600922), *FBN1* (fibrillin; MIM 134797); *TGFBR1* (transforming growth factor-beta receptor, type I; MIM 190181), *TGFBR2* (transforming growth factor-beta receptor, type II; MIM 190182), *SMAD3* (mothers against decapentaplegic, drosophila, homolog of, 3; MIM 603109) and *TGFB2* (transforming growth factor, beta-2; MIM 190220) [Boileau et al., 2012; Guo et al., 2007; Lindsay et al., 2012; Loeys et al., 2006; Pannu et al., 2005; Regalado et al., 2011; van de Laar et al., 2011; Wang et al., 2010; Zhu et al., 2006]. However, there are still many families with this

condition in which the causative gene has not been identified. It is important to note that a subset of these genes mutations also cause additional features, such as the skeletal features in individuals with Marfan syndrome, but other gene mutations can predispose to thoracic aortic aneurysms and dissections without substantial syndromic features. Women with a personal and/or family history of thoracic aortic dissections should be evaluated for mutations in these known genes. If a causative gene mutation is not identified in the family, then women who are at risk of inheriting the genetic predisposition to aortic disease should undergo aortic imaging, preferably prior to pregnancy, and be carefully monitored for aortic disease whether or not aortic enlargement is present. Young women who experience aortic dissections during pregnancy should be assessed for gene mutations underlying the dissection, whether or not they have features of known syndromes such as Marfan syndrome.

The findings from women with *ACTA2* mutations indicate that pregnancy is associated with an increased risk for ascending and descending thoracic aortic dissections with minimal aortic dilatation. This finding is based on a relatively small number of women in whom the diagnosis of *ACTA2* mutation has not been made and no preventive measures were taken. It is not known how much of this risk can be altered with proper medical management, but the experience in patients with Marfan syndrome indicates the risk for rapid dilatation or dissection is low in carefully monitored women without significant aortic enlargement [Meijboom et al., 2005; Rossiter et al., 1995]. Women with *ACTA2* mutations should be counseled about the risk of aortic dissection with pregnancy, including risk of dissection with minimal aortic dilatation. Blood pressure should be carefully monitored in these women, and treatment with β -adrenergic blocking agents considered. Prophylactic repair of the ascending aorta should be considered in women with *ACTA2* mutation who are planning a pregnancy, in particular if the ascending aorta is significantly enlarged, and it is important to note that there is a risk for dissection involving the distal thoracic aorta even after replacement of the ascending aorta. Women with *ACTA2* mutations should be advised to wear medical alert bracelets at all times that indicate a risk of thoracic aortic dissection, stroke and myocardial infarction. Consideration should be given to being near a tertiary care facility with 24-hour cardiovascular surgical coverage at least during the third trimester of pregnancy and a month postpartum. Physicians and patients should be aware of the symptoms of aortic dissections, as well as atypical presentations [Harris et al., 2011]. Pregnant women who present with these symptoms and report a genetic predisposition or family history of aortic aneurysm or dissection should raise a suspicion for aortic dissection and should be evaluated immediately with CT imaging.

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Figure 1.

Contrast-enhanced axial CT images of the chest showing dissection in the ascending aorta measuring 4.2 cm in Patient 2 (A); dissecting aneurysm arising from the aortic root measuring 4.7 cm in Patient 7 (B); and ascending aortic dissection measuring 3.8 cm in Patient 8.

Figure 2.

Aortic pathology of women with *ACTA2* mutations and peripartum aortic dissections. (A) Compared with the control aorta, H&E and Movat staining of the aortic media from Patients 2, 7 and 8 showed mild medial degeneration characterized by focal proteoglycan accumulation (stained blue by Movat staining) and loss of SMCs and elastic fibers (stained black by Movat staining). (B) Movat staining demonstrated occlusion of vasa vasorum (arrow) in Patient 7 which is absent in the control.

Table 1
Disease presentation, management, and outcome of women with ACTA2 mutations and peripartum aortic dissections.

Patient	ACTA2 mutation	Age	Gestational status	Obstetric history ^a	Type of dissection	Symptoms	Diagnostic imaging	Aortic diameter ^b	Obstetric procedure	Cardiovascular procedure	In-hospital complications	Other medical history
1	p.Arg29His	35	9 days postpartum	G1P1	Type B	Chest, back pain; HTN	CT	NA	Emergency cesarean	None	Pre-eclampsia	None
2	p.Arg39Cys	30	28 weeks gestation	G4P2	Type A	Headache; visual changes; facial, pedal edema; HTN; epigastric pain	CT	4.2 cm (ascending, CT)	Emergency cesarean; hysterectomy	Replacement of ascending aorta	HTN	Toxemia
3	p.Met49Val	35	28 weeks gestation	G3P2	Type A	Back pain; syncope; absent femoral pulses	TEE	NA	Emergency cesarean	Femoral thrombectomy; femoral-femoral bypass; replacement of ascending aorta	Multiple organ failure; postpartum pre-eclampsia; coagulation abnormalities; death	None
4	p.Arg149Cys	29	1 week postpartum	G4P4	Type A	NA	NA	NA	Vaginal delivery	Failed repair	Cerebral thrombosis; death	HTN
5	p.Arg149Cys	30	2 weeks postpartum	G3P3	Type B	NA	NA	NA	Vaginal delivery	Replacement of abdominal aorta	NA	MI
6	p.Arg149Cys	37	31 weeks gestation	G1P0	Type A	Chest pain; hypotension; diaphoresis; shortness of breath; nausea	Cardiac catheterization	NA	Emergency cesarean	Failed repair	Death	None
7	p.Gly275Ala	43	37 weeks gestation	G2P0	Type A	Neck pain; throat tightness; epigastric pain; vomiting	TTE, CT	4.7 cm (aortic root, CT)	Emergency cesarean	Replacement of ascending aorta, resuspension of the aortic valve	None	MI; HTN; gestational diabetes
8	p.Ser302Ala	37	6 days postpartum	G3P2	Type A	Chest, jaw pain; blurred vision; syncope	CT	3.8 cm (ascending, CT)	Elective cesarean	Replacement of ascending aorta and transverse aortic arch	Neurological deficits; stroke	None

^a G-gravida; # of pregnancies, P-para; # of delivered pregnancies at disease presentation;

^b aortic diameters are provided in cm and the anatomic location with widest diameter and imaging modality used for measurement are in parenthesis; *HTN*, hypertension; *MI*- myocardial infarction; *TEE*- transesophageal echocardiogram; *TTE*- transthoracic echocardiogram; *CT*- computed tomography; *NA*- data not available.